

Environmental Contaminants and Female Reproductive Capacity



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- Reproductive trends
- Trends/consequences of chemical production
- Exposures and windows of susceptibility
- Effects of environmental contaminants on reproduction
- Working towards solutions

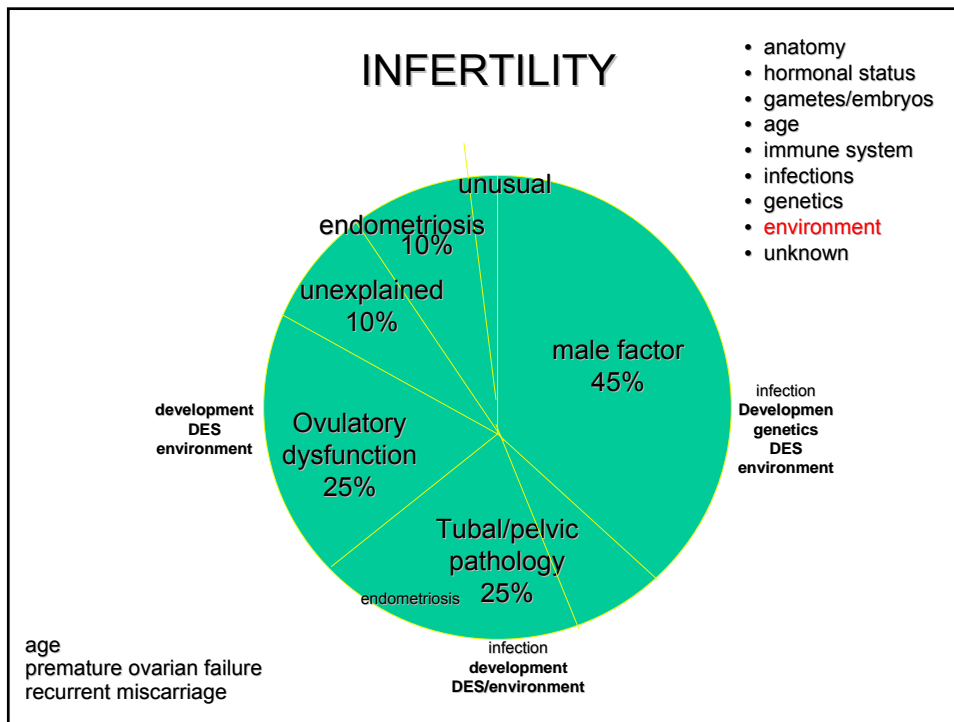
Change in Percent of Impaired Fecundity in the U.S. over 20 Years

2002 - 12%
 1995 - 10%
 1988 - 8%
 1982 - 8%


National Survey for Family Growth
 National Center for Health Statistics
 2002

Age of women	1982	1988	1995	2002	% change (1982-02)
15-24	4.3	4.8	6.1	8.3	+90%
25-34	10.0	9.6	11.2	10.6	
35-44	12.1	10.6	12.8	11.5	
Total	8.4	8.4	10.2	11.8	+40%


Swann, Hertz-Picciotto. Family Planning Persp 1999;31:156-157
 Schettler. Infertility and related reproductive disorders, 2003 online:
<http://www.protectingourhealth.org/newscience/infertility/2003-04peerreviewinfertility.htm>




Environmental Contaminant Effects on Reproductive Health and Fertility



Wildlife



Laboratory



Humans

Heavy metals - lead, mercury, cadmium, arsenic

Solvents * EDC

* **Pesticides** DDT, methoxychlor (HPTE), dimethoate, chlordecone, lindane,

* **Dioxins**

* **PCBs** (electrical transformers) and their metabolites

* **PBDEs** (flame retardants, computers, furniture, clothes, carpets).

* **PVCs and plastics**

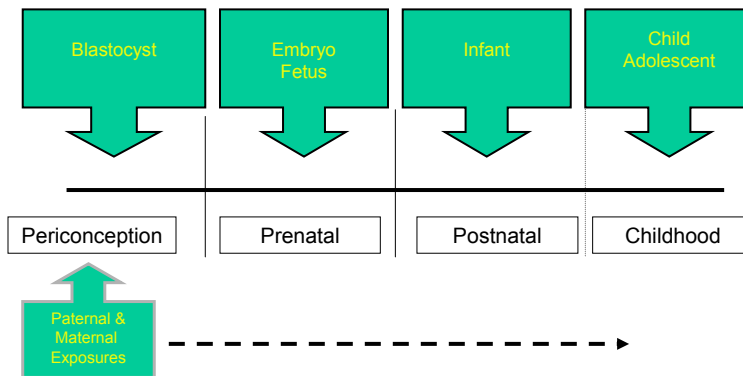
phthalates - plasticizers to soften plastics (shower curtains, vinyl floor coverings, plastic wraps, makeup, lotions, shampoos, nail polish, adhesives, IV bags, building materials, gelatin pill capsules).

bisphenol A - plastic monomer in hard polycarbonates: sports bottles, baby bottles, dental sealants, food and milk carton lining, CD covers, glasses, lenses.

PFCs in Teflon

Air pollution

Critical Windows of Susceptibility



Programming ("Barker Hypothesis"): fetal origins of adult disease.
 Process in which a stimulus or insult at a critical/sensitive period in development or perinatal life has permanent effects on structure, physiology, and metabolism. Godfrey and Barker 2001

Endocrine Disrupting Chemicals (EDCs)

- "an exogenous agent that interferes with synthesis, secretion, transport, metabolism, binding action, or elimination of hormones that are present in the body and are responsible for metabolic homeostasis, reproduction, and developmental process."

EDCs and Reproductive Potential



- Puberty
- Menstruation
- Endometriosis
- Time-to-pregnancy
- Pregnancy loss
- Reproductive senescence
- Sperm counts, quality

US. EPA 1998; Safe et al, 1991; DeRosa et al, 1998; Sonnenschein & Soto 1998; Toft et al 2004



Human Studies

Environmental Exposures: Women

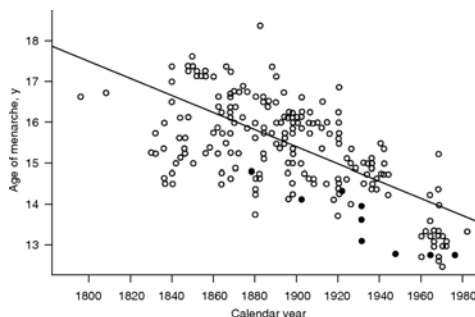
- Increased fetal loss, stillbirth and birth defect syndrome close to agricultural areas sprayed with pesticides (Bell, et al, 2004).
- Early breast development linked to EDCs (2008) (Intn'l adoption)
- In utero exposures:
 - to DDT have longer TTP (Cohn 2003).
 - to DES have a higher incidence of vaginal cancers, infertility, ectopic pregnancy, pre-term delivery, endometriosis, and uterine fibroids (**more today**).
- Pthalates in women are now linked to preterm birth and precocious puberty (Shearle and Franks 2004; Xue et al 2006).
- PCBs, other organochlorines, and fine particulate matter are linked to LBW and prematurity (Bobak 2000)

Other Reproductive/Tract Trends in U.S. and Worldwide

❖ Compared to 30 years ago:

- 20% more babies are born prematurely
- 25% more women get breast cancer
- 45% more men get testicular cancer
- 76% more men get prostate cancer

Age of Menarche in Europe and the US from 1790 to 1980



Euling, S. Y. et al. *Pediatrics* 2008;121:S167-S171

❖ NCI, 2004; Bray et al *Intl J Cancer* 2006; 118:3099; Sokoloff et al, *J Urol* 2007;:177:2030; Penson et al *J Urol* 2007, 2020; Martin et al, 2007 National Center Health Statistics; Davidoff et al *Semin Penatol* 2006;30:8; Stillman et al, *Repro Sci* 2008.

ETS and Adverse Reproductive Effects in Humans



- Reduced fecundity (decreased ovarian reserve)
- Decreased success rates in IVF
- Earlier menopause (by 1-4 years)
- ARH receptor-mediated apoptosis of oocytes
- Increased SAB rate
- *Decreased fertility in daughters of smokers: transgenerational.*

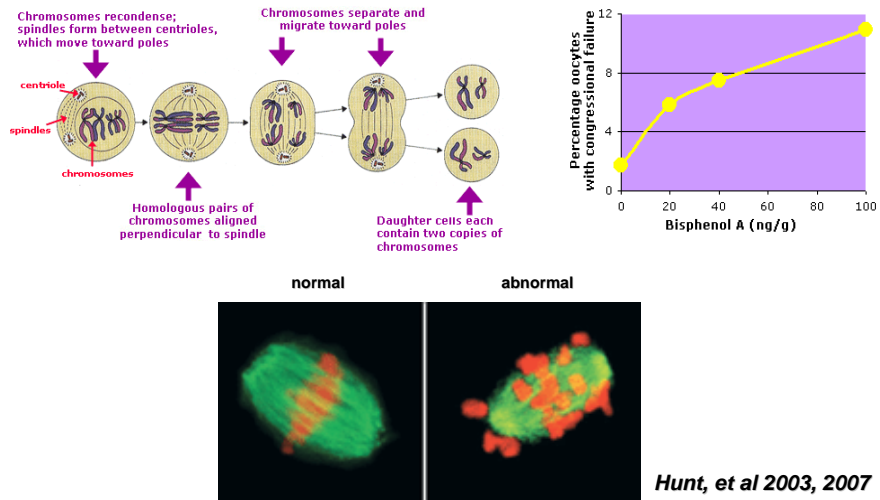


Sharara et al, *Fertil Steril* 1988; Genuis, *Human Repro* 2006

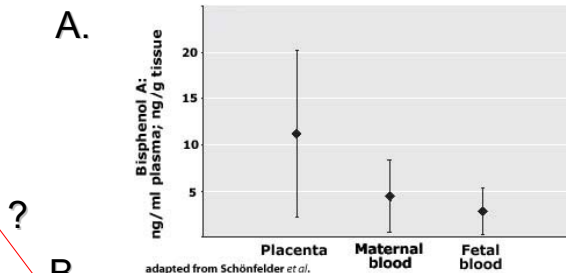
Bisphenol A Causes Aneuploidy



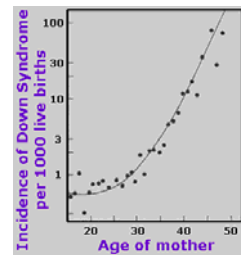
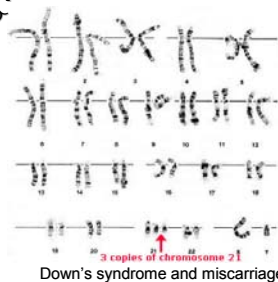
in Offspring of Exposed Dams
and is Transgenerational



Background Exposure to Bisphenol A and Aneuploidy in Humans



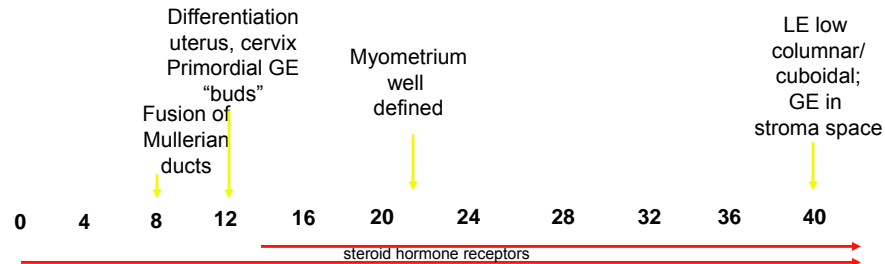
in utero



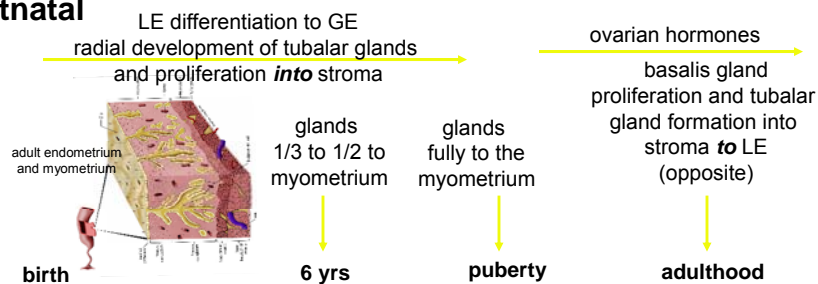
Development of Human Uterus

uterine differentiation is a *pre-* and *post-natal* event

Prenatal



Postnatal



In Utero DES Exposure and Uterine Development

- changes in expression of Wnt 7A, Hoxa10, Hoxa11- genes involved in tissue patterning and demonstration of altered uterine morphogenesis (Ma et al, 1998; Miller et al 1998; Block et al, 2000).
- DES-induced developmental programming requires ER α , suggesting that this signaling is important to establish developmental programming (Couse et al, 2001).
- DES daughters have abnormal vaginal adenosis (Jeffries et al, 1984)
- vaginal adenosis was also found in 80% of stillborns and neonates exposed in utero to DES in the first (Johnson et al, 1979).

Thus, the pre- and perinatal period is a susceptible window during which inappropriate EDCs can induce developmental programming and increase risk for FRT disorders.

Endometriosis

– **Benign gynecologic disorder associated with pelvic pain and infertility**
(glands and stroma outside uterine cavity)

– **Estrogen-dependent**

- primarily in women of reproductive age
- some in post-menopause
- rare in men

– **Prevalence**

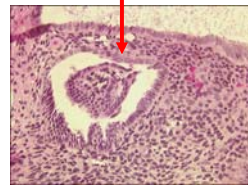
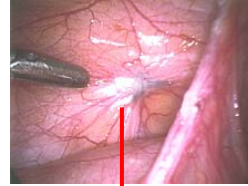
- 6% to 10% of women in general
- 50-60% of women with pelvic pain
- 20-50% of women with Infertility
- 25% of women with endometrioid ovarian cancer

– **Diagnosis: surgical** (US 11 yrs; UK 8.5 yrs)

– **2002** total health care costs estimated in US Dx Rx \$22B

• **All women have retrograde menstruation, but not all women have endometriosis.**

- Local synthesis and decreased metabolism of E_2
- Hypomethylated genes governing E_2 synthesis and ER β expression
- Decreased PRA, PRB
- Resistance to action of progesterone



National Center for Health Statistics. 1987.

• Giudice LC, Kao LC, 2004.

• Simeons et al, 2007

• Burney R, Giudice LC, 2008.

Enhanced sensitivity to E_2

Promotion of Endometriosis by Organochlorines (OCs)

Dioxin (TCDD)

pesticides -methoxychlor and DDT

polychlorinated biphenyls

- Evidence is overwhelming in *adult* laboratory animals that endometriosis can be promoted by many OCs.
- Data linking OC exposure and endometriosis in adult women are equivocal.

Weaknesses of observational epidemiology studies

Limited sample sizes

Confounding variables.

- Data linking in utero exposure to DES and endometriosis in adult women are compelling.

Non-Human Primate Studies of Dioxin and Endometriosis



Rhesus monkeys (*Macaca mulatta*)

Rier et al., Fundam Appl Toxicol 1993

Study design:

20 rhesus monkeys: 6 control arm (0ppt) 7 low dose (5 ppt) arm, 7 high dose (25 ppt) arm. Daily dietary treatment of adults with TCDD for 4 years and followed for 11 subsequent years.

Significant dose-dependent increase in incidence and endometriosis severity

Criticisms: (Guo 2004)

- inappropriate statistical analysis due to low sample sizes and no statistical normality
- many confounders (e.g., parity)
- retrospective addition of endometriosis as an outcome.

However: In cynomolgus monkey (*Macaca fascicularis*) implants of endometrial tissue in the pelvic cavity survived longer and grew larger in animals exposed for one year to high doses of TCDD (17.86 ng/kg/day) (Yang et al, 2000)

Conclusion: Dioxin can promote endometriosis in primates.

Nurses' Health Study II & Endometriosis

Prospective cohort study

- 116,678 female nurses
- Baseline questionnaire in 1989
- Age range in 1989 = 25 – 42 yo
- Follow-up in 2-year intervals

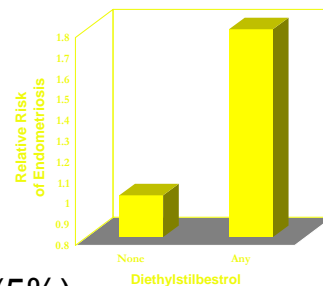
Prevalence at baseline = 6,203 (5%)

Incidence: 2,941 laparoscopically confirmed cases

Pain symptoms prompted diagnosis = 77%

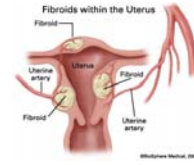
Infertility work-up prompted diagnosis = 23%

- * Exposure to DES: 80 % increased risk of endometriosis
- * Low birth weight
- * Earlier menarche



Missmer et al., Fertil Steril 2004

Uterine Fibroids



- Benign tumors of uterus
 - most common neoplasm in women
 - smooth muscle and ECM proteins collagen and elastin
- Cumulative incidence 30% in women 25-45 y.o.
- Epidemiology
 - Grow in women of reproductive age
 - African American women at higher risk (50% cf. 25% of white women have fibroids); have fibroids at younger age and more of them
 - Increased risk with increasing BMI, early menarche.
 - Decreased risk with cigarette smoking, OCP use, increasing parity
- Pathogenesis: Hormonal, genetic, environmental
- Cost to health care system: surgical (inpatient) costs ~ \$2B in 1997
- Leading cause of hysterectomy:
 - 30% of hysterectomies in white women
 - > 50% of hysterectomies in African American women
- Symptoms and Associations
 - abnormal uterine bleeding
 - dysmenorrhea
 - non-cyclic pelvic pain
 - infertility

Kjeruff et al, 1996
Marshall et al. 1997, 1998a,b
AHRQ Publication # E021, 2001

In Utero DES Exposure and Uterine Fibroids in Humans

- Do DES daughters have an increased incidence of leiomyomata?
- 2 studies - different conclusions:
 - Wise et al 2005: 2,579 women (1,731 exposed, 848 unexposed). No association ($p=0.68$) between prenatal DES exposure and uterine fibroids when histologic confirmation after surgical removal of fibroids was used as the detection criteria.
 - Baird & Newbold 2005: (1,188 women). Significant relationship (OR-2.4, CI 1.1-5.4) between DES exposure and uterine fibroid presence detected by ultrasound.

Prenatal estrogenic exposures may contribute to development of uterine fibroids in women.

It may need a genetic context in which to occur, based on the rodent model data

Environmental Contaminants, Endometriosis and Uterine Fibroids

Summary and Conclusions

The bulk of experimental and epidemiologic evidence supports critical windows of exposures to EDCs and development of female reproductive disorders:

- A role of in utero exposure to EDCs (xenoestrogens) and the development of endometriosis and uterine fibroids in women and select animal models.
- A role of postnatal exposure to xenoestrogens and the development of uterine fibroids.
- A role of adult exposures to EDCs (dioxins, PCBs) in promoting endometriosis growth and uterine fibroid growth.

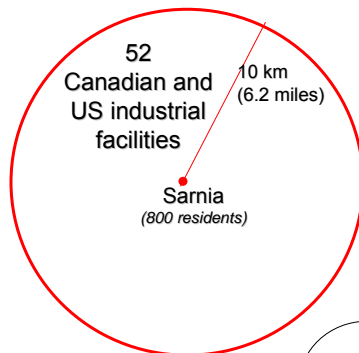
Animal models are important in assessing the role of EDCs on human reproductive tract development and function, noting that differences in timing of developmental milestones may differ from one species to another, but the genetic mechanisms are conserved.



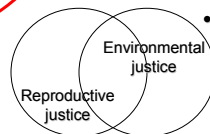
Chemical Valley

“We thought it was normal. We thought that 7 miscarriages was normal. We thought our shoes turning orange in the spring from the melting snow and chemicals landing on the grass was normal. It is not.”

Ronald Plain, Aamjiwnaang First Nation



- 10M kg (23M lbs) chemicals/yr associated with reproductive and developmental problems
- 410K kg (900K lbs) chemicals cause cancer and are EDCs.
- 40% risk of SAbS (25%)
- 2004: sex ratio 2:1 (girls: boys)



EDCs and Sex Ratios

Table 1. Effect of EDCs on secondary sex ratio in humans.

EDC Exposure	Offspring Sex Ratio (M:F)	Reference
Paternal, wood preservatives	Decreased	(Dimich-Ward <i>et al.</i> , 1996)
Maternal/Paternal TCDD	Decreased	(Mocarelli <i>et al.</i> , 1996)
Paternal TCDD	Decreased	(Mocarelli <i>et al.</i> , 2000)
Paternal TCDD	Decreased	(Ryan <i>et al.</i> , 2002)
Paternal TCDD	Balanced	(Schnorr <i>et al.</i> , 2001)
Maternal/Paternal Chemical Warfare Agents in west Azarbaijan, Iran	Decreased during war	(Saadat, 2006)
PCBs and PCDFs in cooking oil	Increased, but deviation not statistically significant	(Yoshimura <i>et al.</i> , 2001)
Paternal TCDD	Increased	(Michalek <i>et al.</i> , 1998)
Paternal PCBs	Increased	(Karmaus <i>et al.</i> , 2002)
PCBs in cooking oil	Balanced	(Rogan <i>et al.</i> , 1999)

- 2 females to 1 male ratio confirmed in some Arctic villages
- Some villages have no boys
- Hormone-mimicking chemicals (PCBs specifically) found in mothers' blood is correlated with excess of girls
- Bioaccumulation in Arctic animals
- Similar trends suspected in most of northern hemisphere

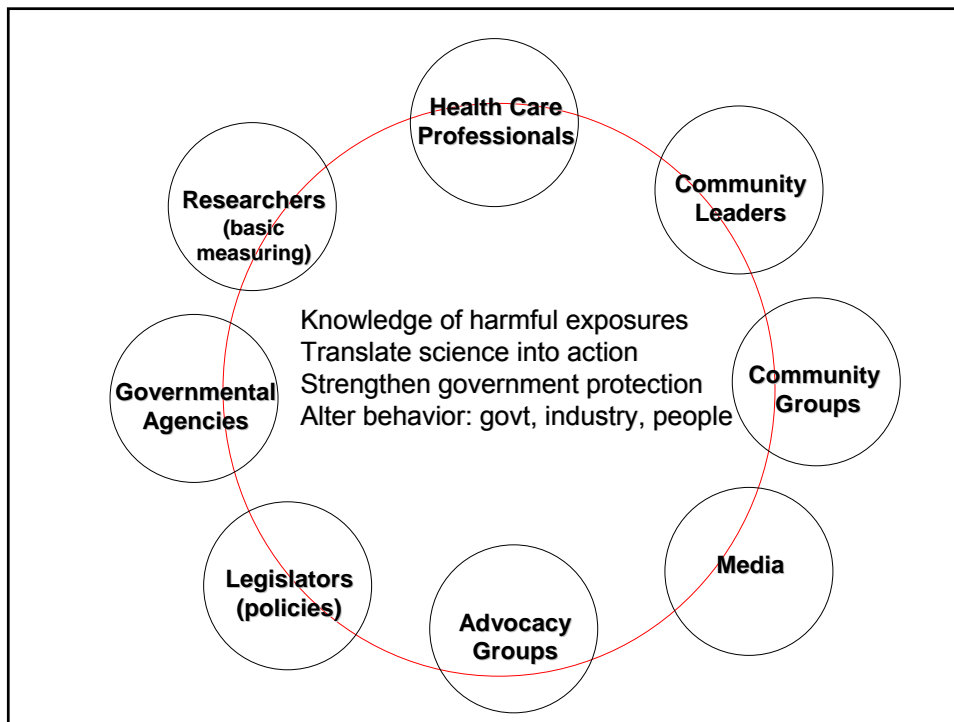


We are in a crisis.

Effective protection from chemical exposures
requires **social action**.

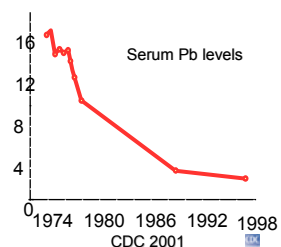
It requires **civic participation** and
environmental education.

- Science not always translatable to humans. Some doubt relevance.
- Gaps in knowledge should not prevent policy actions to prevent harm, as the existing evidence is sufficient to justify such action.
- Examples: EU (Cosmetic Directive 2005, RoHS 2006, WEEE 2006, REACH 2007, Canada, US (California Green Chemistry Initiative/responsible chemical production, use, re-use, other...)
- **It is our moral and social responsibility.**



Next Steps

- The role of women
- Minimize/eliminate chemicals for cleaning or beauty, especially during WoS
- Minimize the use of plastics, recycle
- Do not eat food that does not spoil
- Go back to old traditions
- Slow down
- Less is more
- Precautionary principle
- Guidelines for health care professionals and patients
- Hopefully it is not too late.





Program for Reproductive Health and the Environment

University of California, San Francisco

research, education, advocacy, mentoring, clinical care, ethics, networking
UCSF Children's, Women's, and Cancer **Hospital** at
Mission Bay

Linda C. Giudice, MD, PhD, MSc, UCSF PRHE Founder
Tracey Woodruff, PhD, MPH, UCSF PRHE Director
Alison Carlson, CHE Fertility
Charlotte Brody, Commonweal
Louis Guillette, PhD, University of Florida
Nancy Milliken, MD and Dixie Horning
UCSF Center of Excellence in Women's Health
Fred Gellert Family Foundation